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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,790	02/08/2002	Alison A. McCormick	42254	3922

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,790	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-54 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51,53,54,56 and 57* is/are rejected.

7)☒ Claim(s) *52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Note: Applicant has amended claim 51 to incorporate the language of claim 55. Applicant has subsequently canceled claim 55.

Claims 55 and 68 have been cancelled by Applicant.

Claim 51 has been amended by Applicant.

Claims 51-54 and 56-67 are pending and under examination.

Objections Withdrawn

The objections of claim 51 and 65-67 are withdrawn in view of comments from Applicant concerning claim 51 and the withdrawal of the rejections of the claims in which claims 65-67 depend.

Rejections Withdrawn

The rejections of claims 52 and 55 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of the amendments of the claims.

The rejection of claims 51-64 under USC 103(a) is withdrawn in view of Applicant's amendment incorporating the language of claim 55 into claim 51 and Applicant's persuasive remark that the vaccine of the instant application produces an

immune response in the absence of an adjuvant or other immunostimulatory material. Applicant noted that the vaccine described by Hakim et al. (Journal of Immunology, 157 (12):5503-5511, 1996) unsuccessfully attempted this. The self-antigen taught by Hakim et al. required fusion of the antigen to other large proteins or use of naked DNA in order to obtain an immune response.

The following are new grounds for objection:

Claim 56 is objected for being depended upon a canceled claim. Appropriate correction is required.

Claim 52 is objected to as being dependant upon a rejected base claim.

The following are new rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51, 53-54, and 56-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a polypeptide self-antigen useful as a tumor-specific vaccine in a subject with B-cell lymphoma wherein the first domain and the second domain of the polypeptide self-antigen are

encoded by at least in part by a nucleic acid in the cells of said B-cell lymphoma, which polypeptide comprises two peptide domains connected to each other by a peptide linker, and said polypeptide includes an epitope or epitopes unique to, or overexpressed by cells of said B-cell lymphoma, thereby distinguishing said B-cell lymphoma from normal cells and/or all other tumors (i) of the same or different histological type, (ii) in said subject or in another subject or in another member of said subject's species, comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct; (b) joining the first nucleic acid construct encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporating said second nucleic acid construct into a plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the linker; (d) transfecting the plant with the vector so that the plant is capable of producing the polypeptide; (e) producing the polypeptide; and (f) recovering the polypeptide as a soluble, correctly-folded protein, wherein the polypeptide recovered from said plant or plant cell is in correctly folded form, without a need for denaturation and renaturation and mimics said epitope or epitope in their native form and is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials, so that administration of said polypeptide results in an antibody or cell-mediated immune response to said epitope or epitopes and wherein the polypeptide is a single chain wherein the first domain is the Ig V_H domain and the second domain is the

Ig V_L domain, both of which domains create an idiotype of a surface Ig of a B cell lymphoma, and wherein said polypeptide induces an idiotype-specific response directed to said lymphoma upon administration to a subject, does not reasonably provide enablement wherein the first domain and the second domain of the polypeptide self-antigen are encoded by at least in part by a nucleic acid in the cells of any and all types of tumors, which polypeptide comprises two peptide domains connected to each other by a peptide linker, and said polypeptide includes an epitope or epitopes unique to, or overexpressed by cells of any and all types of tumors, thereby distinguishing a tumor from normal cells and/or all other tumors (i) of the same or different histological type, (ii) in said subject or in another subject or in another member of said subject's species, comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct; (b) joining the first nucleic acid construct encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporating said second nucleic acid construct into a plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the linker; (d) transfecting the plant with the vector so that the plant is capable of producing the polypeptide; (e) producing the polypeptide; and (f) recovering the polypeptide as a soluble, correctly-folded protein, wherein the polypeptide recovered from said plant or plant cell is in correctly folded form, without a need for denaturation and renaturation and mimics said epitope or epitope in their native form and is capable of inducing an immune response in a

mammal, including said subject, without a need for adjuvant or other immunostimulatory materials, so that administration of said polypeptide results in an antibody or cell-mediated immune response to said epitope or epitopes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This is a **scope of enablement rejection**.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The instant claims are drawn to method of producing a polypeptide self-antigen useful as a tumor-specific vaccine in a subject with a tumor or at the risk of developing a

tumor. This includes any and every type of tumor and any and every polypeptide self-antigen.

The specification teaches that in a preferred embodiment the polypeptide is derived from, and mimics, surface Ig of a B-cell lymphoma and includes one or more idiotopic determinant of that Ig that is uniquely characteristic of that lymphoma (page 8, in particular). The specification further teaches that in a preferred embodiment, the immunogenic self-protein is a single chain antibody that includes the V_H and V_L regions of the unique surface Ig of the subject's B-cell lymphoma, and which is sufficiently immunogenic to induce a detectable immune response in that subject to his B-cell lymphoma (page 8, in particular). The specification is silent on methods describing how one would make polypeptide self-antigens to tumors other than B-cell lymphomas.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods of making a polypeptide self-antigen useful as a tumor specific vaccine for every cancer with a multitude of possible self-antigens, and applicant has not enabled all of these types of proteins because it has not been shown that these proteins can be created or are capable of functioning as to that which is being disclosed.

With regards to making and using any and all polypeptide self-antigens, those of skill in the art recognize that protein chemistry is probably one of the most unpredictable

areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138; 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2).

With regards to the predictability of producing self-antigen vaccines against tumors, those of skill in the art recognize that treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents. Indeed, since

formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, Bodey et al. (Anticancer Research, 2000, 20:2665-2676) teach that there are significant limitations for cancer vaccines. Limitations taught by Bodey et al. include the possibility of faulty antigen presentation which could result in tolerance induction to the antigen, and subsequent rapid tumor progression (page 2665, in particular). Bodey et al. further teach that general immune activation directed against the target antigens has not been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a period of remission (page 2665 right column, in particular). Further, Bodey et al. teach the major deficiency of cancer vaccines to fulfill their promise is due to a natural enrichment of clones of highly aggressive neoplasticlaly transformed cells, which are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular antigen subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use. (page 2665 right column, in particular). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Reasonable correlation must exist between the scope of the claims and scope

of enablement set forth, and it cannot be predicted from the disclosure that all such polypeptides self-antigens will function as predicted.

In view of the teachings above and the lack of guidance, workable examples and exemplification in the specification, it would require undue experimentation by one of skill in the art to determine, with any predictability, that the method would function as claimed.

Claims 51, 53-54, and 56-67 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **written description rejection.** In the instant case, the written description is not commensurate in scope with the claims drawn to a genus of "tumor" or a genus of "polypeptide self-antigen".

The written description only reasonably contemplates one species of "tumor" (pages 8-14, in particular) and one species of "polypeptide self-antigen". The only species of tumor contemplated by the written description is B-cell lymphoma; and the only species of polypeptide self-antigen contemplated by the written description is one that can induce an immune response to the idiotype of a B-cell clone or B-cell lymphoma of an individual (pages 16 and 17, in particular). A description of a genus

may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genera. That is, the specification provides neither a representative number of tumors or polypeptide self-antigens that encompass the genera of tumor or polypeptide self-antigens nor does it provide a description of structural features that are common to the claimed tumors or polypeptide self-antigens. Further, the specification provides neither a representative number of tumors or polypeptide self-antigens that encompass the genera of tumors or polypeptide self-antigens along with a description of structural features that are common to the tumors or polypeptide self-antigens. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genera, and because the genera are highly variant, the disclosures of

one species of tumor and one species of polypeptide self-antigen are insufficient to describe the genera. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genera as broadly claimed.

Descriptions of the genera of "tumor" and "polypeptide self-antigen" may be achieved by means of a recitation of a representative number of tumors or polypeptide self-antigens, defined by structure, falling within the scope of the genera. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genera of "tumor" or "polypeptide self-antigen" that would distinguish the claimed "tumor" and "polypeptide self-antigen" from other substances that do not have the claimed biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genera, and because the genera are highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide representative numbers of species to describe and enable the genera as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that

[he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera of "tumor" and "polypeptide self-antigen", and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only B-cell lymphoma tumors and polypeptide self-antigens wherin the first domain is the Ig V_H domain and the second domain is Ig V_L domain, both of which domains create an idiotype of a surface Ig of a B-cell lymphoma, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claim is allowed.

Summary

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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